REMARKS

A check for $595 for the fees for filing of an RCE ($385) and for the fee for a two-month extension of time ($210) accompanies this response. Any fees that may be due in connection with this application throughout its pendency may be charged to Deposit Account No. 06-1050.

In compliance with our duty of disclosure, the Examiner's attention is directed to co-pending U.S. application Serial Nos. 10/317,269 and 10/410,700, allowed U.S. application Serial No. 09/905,501 and allowed U.S. application Serial No. 09/271,575, now U.S. Patent No. 6,602,274. The named inventor of the instant case is the same named inventor of the patent and all of the listed applications. It is noted that if any rejections for obviousness-type double patenting are instituted, then any Action with such rejection cannot be made final.

Claims 1, 4-6, 11, 12, 16, 17, 19-24, 36 and 38-41 are presently pending in this application. Claim 1 is amended to more particularly point out and distinctly claim the subject matter by restating the claim to recite "a conjugate comprising a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium that lines or composes neovascular target tissue," basis for which is found throughout the specification (for example, see paragraphs [042] - [043]). Claim 1 also is amended to include the recitation "allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue," basis for which is found throughout the specification (for example, see paragraph [047]). Claim 1 is further amended to more distinctly claim the subject matter by including the recitation "including a wavelength corresponding at least in part with the characteristic light absorption wavelength of the photosensitizing compound," basis for which is found throughout the specification (*e.g.*, see paragraph [049]).

Claims 11, 16 and 38-40 are amended to include the recitation "targeting moiety" necessitated by the amendment of claim 1 herein. Claim 17 is amended to replace the phrase "targeted photosensitizing compound" with the recitation –conjugate–, necessitated by the amendment of claim 1 herein.

No new matter has been added.

Basis for added claims 42-44 can be found throughout the specification (for example, see paragraph [040]). Basis for added claim 45 can be found throughout the specification (for example, see paragraphs [048] - [050]). Basis for added claims 46-49 can be found throughout the specification (for example, see claims 1 and 22-24 as originally filed). No new matter is added. Accordingly, entry of the amendments to the claims is respectfully requested.

REJECTION OF CLAIMS 1-6, 11-12, 16-24 and 36 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-6, 11-12, 16-24 and 36 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to describe the claimed subject matter in such a way as to enable one skilled in the art to make and use the claimed subject matter commensurate in scope with these claims. The Examiner alleges that the specification (1) provides insufficient guidance as to how to make *any* "targeted photosensitizing compound" for the claimed method; (2) provides insufficient guidance as to the structure and properties of *any* "targeted photosensitizing compound" because there allegedly is insufficient guidance as to which "other agent" that absorbs light in a range of 500nm-1100nm would be useful in the claimed method without undue experimentation; (3) provides insufficient guidance as to the target such as the receptor, antigen, ligand and antibody that binds to the undisclosed antigen on the abnormal endothelium that lines or composes neovascular tissue of the eye; and (4) provides insufficient guidance as to the combination of the intensity of light used for the illumination and the duration of illumination to arrive at the total fluence because there is insufficient guidance for the intensity of light to be used.

The Examiner states that the specification is enabling for the method to treat neovascular disease of the eye including administering a targeted photo-sensitizing compound such as verteporfin conjugated to L19 antibody that binds to the ED-B domain of fibronectin, and benzoporphyrin conjugated to VEGF that selectively binds to abnormal endothelium that lines or composes neovascular tissue and illuminating the neovasculature tissue with light for a period of time sufficient to activate the photosensitizing compound thereby causing damage to neovasculature tissue but without impairing or destroying other tissue. Hence, the Examiner states that the disclosed steps are enabled but are allegedly not commensurate in scope with the claims. The Examiner concludes that one of skill in the art would not be able to practice the claimed methods without an undue amount of experimentation.

This rejection is respectfully traversed.

RELEVANT LAW

The test of enablement is whether one skilled in the art can make and use what is claimed based upon the disclosure in the application and information known to those of skill in the art without undue experimentation. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). A certain amount of experimentation is permissible as long as it is not undue. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. The "invention" referred to in the enablement requirement of section 112 is the claimed subject matter. *Lindemann Maschinen- fabrik v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing

> and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling. . . it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with evidence or reasoning which is inconsistent with the contested statement.

Id. (emphasis in original); *See also Fiers v. Revel*, 984 F.2d 1164, 1171-72, 25 USPQ2d 1601, 1607 (Fed. Cir. 1993);, *Gould v. Mossinghoff*, 229 USPQ 1, 13 (D.D.C. 1985), *aff'd in part, vacated in part, and remanded sub nom. Gould v. Quigg*, 822 F.2d 1074, 3 USPQ2d 1302 ("there is no requirement in 35 U.S.C. § 112 or anywhere else in patent law that a specification convince persons skilled in the art that the assertions in the specification are correct"). A patent application need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent , Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987).

The inquiry with respect to scope of enablement under 35 U.S.C. § 112, first paragraph, is whether it would require undue experimentation to make and use the subject matter as claimed. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims (i.e. the "Forman factors"). *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

PTO GUIDELINES

The PTO has promulgated guidelines, which incorporate the above-noted law, for examining chemical/biotechnical applications with respect to 35 U.S.C.

§112, first paragraph, enablement. As set forth in the guidelines, the standard for determining whether the specification meets the enablement requirement is whether it enables any person skilled in the art to make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1988). In determining whether any experimentation is "undue," consideration must be given to the above-noted factors.

As indicated in the published guidelines, it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The analysis must consider all the evidence related to each of the factors, and any conclusion of non-enablement must be based on the evidence as a whole. *Id.* 8 USPQ2d at 1404 & 1407.

The starting point in an evaluation of whether the enablement requirement is satisfied is an analysis of each claim to determine its scope. The focus of the inquiry is whether everything within the scope of the claim is enabled. As concerns the breadth of a claim relevant to enablement, the only concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). Once the scope of the claims is addressed, a determination must be made as to whether one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation.

It is incumbent upon the Examiner to first establish a *prima facie* case of non-enablement. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369-70 (CCPA 1971). The requirements of 35 USC §112, first paragraph, can be fulfilled by the use of illustrative examples or by broad terminology. *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973):

> ... we do not regard section 112, first paragraph, as requiring a specific example of everything within the scope of a broad claim ... What the Patent Office is here apparently attempting is to limit all claims to the specific examples, not withstanding the disclosure of a broader invention. This it may not do.

In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960) :

> It is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it.

This clause does not require "a specific example of everything *within the scope* of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of § 112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." *In re Marzocchi et al.*, 469 USPQ 367 (CCPA 1971)(emphasis added).

ANALYSIS

The Office Action fails to establish a *prima facie* case of lack of enablement pursuant to 35 U.S.C. § 112, first paragraph for the following reasons.

The Office Action alleges that the claims are enabled only for what applicant has specifically exemplified in the Examples. Applicant respectfully submits that all the possible embodiments for "photosensitizers," "binding pair," "endothelial receptors," "endothelial ligands," "endothelial antigens," "antibodies that selectively bind to abnormal endothelium," and "neovascular disease of the eye" known to one of skill in the art are contemplated to be within the scope of claims. Numerous alternate embodiments are known to those of skill in the art, as evidenced by the references made of record and discussed below. The specification discloses exemplary embodiments of each, as discussed in more detail below.

Applicant respectfully submits that a patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. *Smith v. Snow*, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935). The requirements of 35 USC §112, first paragraph, can be fulfilled by the use of illustrative examples or by broad terminology, and the Patent Office may not limit all claims to the specific examples. *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973). Applicant is entitled to claims that are commensurate in scope not only with what applicant has

specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

The specification recites that the claimed subject matter is directed to a method of photodynamic therapy to treat neovascular disease of the eye that includes administering a conjugate including a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium that lines or composes neovasculature tissue; allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue; and illuminating the neovasculature target tissue with light using a non-coherent light source including a wavelength corresponding at least in part with the characteristic light absorption wavelength of the photosensitizing compound for a period of time sufficient to activate the photosensitizing compound thereby causing damage to neovasculature tissue, where a combination of an intensity of light used for the step of illuminating and a duration of illumination are selected to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Applicant notes that the Examiner states that the exemplified steps **are enabled** in the specification (paper number 01122004, pages 2-3). The mere fact that the precise steps of the embodiment exemplified in the specification are not recited in the claims does not provide sufficient reason to hold the claims non-enabled. The enablement requirement of 112, first paragraph, does not require that the claims recite specific elements for "photosensitizing compound" or "binding pair" or "endothelial antigen or ligand" or a specific "targeting moiety" or even that the specification recite specific elements for all circumstances, when such elements can be readily determined by one skilled in the art using the teachings of the specification. As discussed in detail below, various "photosensitizing compounds" and "binding pairs" and "endothelial antigens" and "endothelial ligands" and "targeting moieties that selectively bind to abnormal endothelium" are known in the art. Reciting precise elements in the claims would be unduly limiting and should not be required.

In this instance, applicant is providing a general method of photodynamic therapy to treat neovascular disease of the eye. To limit the claims to specific elements for "photosensitizing compound" or "binding pair" or "endothelial antigen" or "endothelial ligand" or a specific "targeting moiety that selectively binds to abnormal endothelium" would permit those of skill in the art to practice the claimed method, but avoid infringement, merely by substituting different elements to achieve the same outcome, which are known or could be readily identified using the methods described in the specification and known in the art.

It would not require undue experimentation to use the claimed methods in the treatment of neovascular disease of the eye

As discussed below, the claims are commensurate in scope with the disclosure, which exemplifies particular embodiments within the scope of the claims and teaches how one of skill in the art can practice other embodiments within the scope of the claims. In particular, there is a substantial amount of guidance presented in the specification, the level of skill in the art is high, there are several working examples, and the type of experimentation, in view of the disclosure in the application, is routine. General techniques and conditions for photodynamic therapy are provided in the specification and are known to the skilled artisan, as discussed in detail below, and any necessary adjustment can be determined empirically using routine testing or even based on theoretical calculations. Having taught the requisite result to be achieved — a method to treat neovascular disease of the eye that includes administering a conjugate that includes a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium that lines or composes neovasculature tissue; allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue; and illuminating the neovasculature target tissue with light using a non-coherent light source including a wavelength corresponding at least in part with the characteristic light absorption wavelength of the photosensitizing compound for a period of time sufficient to activate the photosensitizing compound thereby causing damage to neovasculature tissue, where a combination of an intensity of light used for the step of illuminating and a

duration of illumination are selected to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged— it would not require undue experimentation to select appropriate conditions to achieve the desired result. Thus, it would not require undue experimentation for one of skill in the art to make and use the claimed subject matter.

Evaluation of the above Factors

1. The scope of the claims

Claim 1 is directed to a method to treat neovascular disease of the eye that includes administering a conjugate that includes a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium that lines or composes neovascular tissue; allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue; and illuminating the neovascular tissue with light using a non-coherent light source including a wavelength corresponding at least in part with the characteristic light absorption wavelength of the photosensitizing compound for a period of time sufficient to activate the photosensitizing compound; where a combination of an intensity of light used for the step of illuminating and a duration of illumination is selected to produce a total fluence of irradiation such that the neovascular target tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Claims 4-6, 11-12, 16-24, 36 and 38-41 all ultimately depend from claim 1 and are directed to various embodiments thereof.

The claimed subject matter is directed to methods of photodynamic therapy (PDT) to treat neovascular disease of the eye using photosensitizing compounds that are conjugated to a targeting moiety that selectively binds to abnormal endothelium that lines or composes neovascular tissue in the eye. The components used in the methods are known to one skilled in this art. The instant claims are directed to methods of administering these components in a photodynamic therapy to treat neovascular disease of the eye based on targeting the photosensitizing compounds to abnormal endothelium that lines or composes

neovascular tissue in the eye and the activation of these targeted photosensitizer compounds by subsequently administering to the subject a combination of an intensity of light used for the step of illuminating and a duration of illumination selected to produce a total fluence of irradiation such that the neovascular target tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

2. Level of skill in the art

In this instance, the level of skill in the art is high. This is evidenced by the art in this area, which is authored primarily by those with Ph.D. and M.D. degrees and is intended for an audience of similarly highly skilled individuals, primarily in the fields of biochemical, pharmaceutical, or medical arts. The numerous articles and patents made of record in this application, authored and reviewed by those known in the art, address a highly skilled audience, and further evidence the high level of skill in this art. In fact, the prior art indicates that the first use of photodynamic therapy was in 1966 (T. J. Dougherty, *Seminars in Surgical Oncology* 2:24-37 (1986)), and that studies in the 1970s and 1980s were directed to using porphyrins and chlorins for treatment of hyperproliferative and neoplastic vascular tissue (Williams *et al.* (U.S. 5,576,013; 1996). The age of the cited art is a strong factor supporting the view that the skilled artisan would have been familiar generally with use of photosensitizing compounds in photodynamic therapy for treatment of neovascular tissues. Therefore, the amount of disclosure required to meet the enablement requirement is minimal.

3. State of the Art

At the time of filing of the instant application, a broad body of knowledge had amassed in the areas of pharmaceutical sciences, medicine, and biochemistry directed to the use of photodynamic therapy as a treatment for hyperproliferative tissues such as neovascularization. Many of these articles and patents have been made of record in this application. For example, Pandey *et al.* (*J Molecular Recognition* 9:118-122 (1996)) discloses that photodynamic therapy is "a well recognized treatment for the destruction of tumors which utilizes the ability of a

selectively retained photosensitizer to elicit an efficient photodynamic reaction upon activation with light." Many photosensitizing compounds were known to those skilled in this art at the time the application was submitted, including hematoporphyrins, porphyrins, chlorins, bacteriochlorins, benzoporphyrins, phthalocyanines, metallo-phthalocyanines and purpurines and their derivatives; naphthalocyanines, texaphyrins, porphycenes, platyrins and other extended tetrapyrroles (Kreimer-Birnbaum, *Sem Hematol. 26(2)*: 157-173 (1989)).

Richter *et al.* (U.S. Patent No. 5,770,619) discloses photosensitizing compounds including merocyanines, pheophorbides, psoralens, monoaspartyl chlorin, zinc phthalocyanine, tin etiopurpurin and porfimer sodium, and pro-drugs such as δ-aminolevulinic acid which can produce drugs such as protoporphyrin in tissue. Additional PDT agents derived from natural sources are disclosed in U.S. Pat. Nos. 4,961,920 (Ward, 1990), 4,861,876 (Kessel, 1989) and 4,753,958 (Weinstein *et al.*, 1988). Other known PDT agents include pyrromethane boron difluorides, indocyanine green, zinc phthalocyanine, rose bengal, epigallocatechin, epicatechin derivatives, hypocrellin B, urocanic acid, indoleacrylic acid, rhodium complexes, etiobenzochlorins, octaethylbenzochlorin, sulfonated Pc-naphthalocyanine, chloroaluminum sulfonated phthalocyanine, iminium salt benzochlorins and other iminium salt complexes, Merocyanin 540, Hoechst 33258, acridine compounds, suprofen, tiaprofenic acid, furocoumarin hydroperoxides, Victoria blue BO, methylene blue and toluidine blue (U.S. Patent No. 5,576,013 (Williams *et al.*, 1996)). Kessel *et al.* (*Photochemistry and Photobiology 58(2)*: 200-203 (1993) discloses assays useful as predictive of the efficiency of photosensitizing compounds in photodynamic therapy. Henderson *et al.* (Cancer Research 57: 4000-4007 (1997) teaches that tumor cell photosensitization, tumor response and vascular photosensitization are linked through common mechanisms. Chlorins and porphyrins have been used in photodynamic therapy as a treatment for diseases associated with hyperproliferation and neovascularization and for occluding neovascularizations (Schmidt-Erfurth *et al.*, *Lasers in Surgery and Medicine* 17: 178-88 (1995)).

These references to numerous published protocols for photodynamic therapy, for identifying, producing and/or extracting photosensitizing compounds, and using such compounds to treat a variety of hyperproliferative tissues, including neovascular tissue, demonstrate the large volume of information regarding tested and reliable procedures available at the time of filing of the application, and thus evidence the state of the art at the relevant time.

4. Teachings in the Specification and Presence of Working Examples

Structure or Function of Photosensitizing Compound

The Examiner alleges that the specification provides insufficient guidance as to the function and structure of the targeted photosensitizing compound. The applicant respectfully disagrees. The specification provides a detailed amount of direction and guidance for selection of a photosensitizing compound that is encompassed in the claims. For example, paragraph [036] discloses that

> a photosensitizing compound is a chemical compound which homes to one or more types of selected target cells and, when contacted by radiation, absorbs the light, which results in impairment or destruction of the target cells. Virtually any chemical compound that homes to a selected target and absorbs light may be used in this invention. Preferably, the chemical compound is nontoxic to the subject to which it is administered or is capable of being formulated in a nontoxic composition. Preferably, the chemical compound in its photodegraded form is also nontoxic.

The specification teaches that the function of the photosensitizing compound is to generate singlet oxygen and other reactive species when the photosensitizing compound absorbs light at a wavelength which closely matches the absorption spectra of the photosensitizer (paragraph [005]), which results in impairment or destruction of the target cells (paragraph [036]). The applicant respectfully submits that a patent application need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent , Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987). The function of a photosensitizing compound in photodynamic therapy is well known to those skilled in the art (for example, see Dougherty *et al.*, *Proc. Int. Symp. Porphyrins Tumor Photother.*, Milan, 16-18 May 1983; Sternberg *et al.*, *Tetrahedron 54*: 4151-4202 (1998)).

As to the alleged lack of sufficient guidance in the specification regarding the structure of the photosensitizing compound, applicant respectfully submits that the instant claims are not directed to any specific photosensitizing compound, but are directed to particular methods of using such compounds to treat neovascular disease of the eye. Therefore the structure of the photosensitizing compound is not relevant to patentability since any photosensitizing compound is contemplated for use in the claimed methods. Notwithstanding this, the specification teaches that the photosensitizing compound absorbs light in the range of 500 nm - 1100 nm and that virtually any chemical compound that is activated by light in this range and functions as a photosensitizing compound as discussed above and known to one of skill in this art may be used in the claimed method, and directs the skilled artisan to a comprehensive listing of photosensitive chemicals found in Kreimer-Birnbaum, Sem. Hematol. 26:157-73, (1989) (see paragraph [012]), the teachings of which are incorporated in their entirety by reference (see paragraph [036]). The specification also includes specific teaching of the structure/function of indocyanine green, pyropheophorbide compounds and alkyl ether analogs of chlorins, and specifically incorporates by reference in their entirety the teachings of WO 92/00106 (Raven *et al.*); WO97/31582 (Abels *et al.*); Devisselle *et al.*, *SPIE* 2627:100-108 (1995); U.S. Patent No. 5,459,159; U.S. Patent No. 5,955,585; and U.S. Patent No. 5,952,366 (see paragraph [040]).

Further, the specification provides exemplary photosensitizing compounds, including any one or combination of chlorins, bacteriochlorophylls, phthalocyanines, porphyrins, purpurins, merocyanines, psoralens, benzo-porphyrin derivatives (BPD), porfimer sodium, indocyanine green (ICG), methylene blue, toluidine blue, texaphyrins and pro-drugs such as δ-amino-levulinic acid, which can produce drugs such as protoporphyrin (see paragraph [036]), and pyropheophorbide compounds, bacteriochlorophyll derivatives, alkyl ether analogs of chlorins (see paragraph [040]).

The specification also teaches the requisite properties for photodynamic therapy. For example, the specification teaches that the photosensitizing

compounds have a light absorbance in a range of 500 to 1100 nm (paragraph [036]). The specification teaches methods of administering the photosensitizing compound (paragraph [046]). The specification teaches that the use level of the photosensitizing compound can be determined clinically (paragraph [047]) and provides exemplary use levels between about 5 mg/m^2 (paragraph [054]) and about 25 mg/m^2 (see paragraphs [061] and [064]). The specification teaches that the duration of illumination will be determined empirically but is preferably a total or cumulative period of time between 4 minutes and 148 hours (paragraph [048]). The specification also teaches that the total fluence of the light is between 30 Joules and about 25,000 Joules (see paragraph [049]) using an intensity of light substantially less that 500 mW/cm^2, where a combination of an intensity of light used for illuminating and a duration of illumination are selected to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged (see paragraph [[050]). The specification teaches how to evaluate the effectiveness of the method in treating neovascular disease of the eye, such as standard visual acuity testing, ophthalmoscopy, color fundus photography and stereo fluorescein angiography (see paragraphs [053] and [057]).

The specification provides several working examples illustrating exactly how to use various photosensitizing compounds in the claimed methods for treating neovascular disease of the eye. Specifically, EXAMPLE 1 provides details of exemplary *in vivo* biological studies using as the photosensitizing compound verteporfin conjugated to a bindable fragment of the L19 antibody demonstrating high affinity to the ED-B of fibronectin in a method to treat choroidal neovasculature lesions (see paragraphs [053] - [057]). EXAMPLE 2 provides details of exemplary *in vivo* biological studies using as the photosensitizing compound a benzoporphyrin derivative conjugated to VEGF in a method to treat retinal neovasculature lesions (see paragraphs [058] through [060]). EXAMPLE 3 provides details of exemplary *in vivo* biological studies using as the photosensitizing compound texaphyrin conjugated to antibody elicited to $\alpha v\beta 3$ in a

method to treat vascular tumors of the eye (see paragraphs [061] and [062]). EXAMPLE 4 provides details of exemplary *in vivo* biological studies using as the photosensitizing compound both texaphyrin conjugated to antibody elicited to $\alpha v\beta 3$ and a benzoporphyrin derivative conjugated to an antibody elicited to carcinoembryonic antigen in a method to treat choroidal tumors of the eye (see paragraphs [063] through [066]).

Therefore, in light of the high level of skill in the art, the extensive teachings regarding photosensitizing compounds in the art, and the teachings of the specification, which provides at least 17 exemplars of photosensitizing compounds from various chemical classes, and which provides several working examples of photosensitizing compounds used in exemplary *in vivo* methods, it is respectfully submitted that it would not require undue experimentation for a skilled artisan to select a photosensitizing compound for use in the claimed methods.

How to Make *Any* "Targeted Photosensitizing Compound"

The Examiner alleges that the specification provides insufficient guidance as to how to make *any* "targeted photosensitizing compound." Applicant respectfully submits that the instant claims are not directed to any specific photosensitizing compound, but are directed to particular methods of using such compounds to treat neovascular disease of the eye. None of the claims are to methods of making a photosensitizer compound. A photosensitizing compound known to one skilled in this art is **selected** for use in the claimed method.

As discussed above, there are many photosensitizing compounds known to those skilled in this art. The specification discloses a number of exemplary photosensitizing compounds (see, for example, paragraph [040]). Further, the specification directs the skilled artisan to a comprehensive listing of photosensitive chemicals found in Kreimer-Birnbaum, Sem. Hematol. 26:157-73, (1989) (see paragraph [012]), the teachings of which are incorporated in their entirety by reference (see paragraph [036]). Further, the literature in the field at the time of application was replete with methods of making photosensitizing compounds. Many of these references have been made of record. For example, Levy *et al.* (US

5,283,255, February 1, 1994) discloses methods for preparing hydro-monobenzo-porphyrins. Pandey *et al.* (US 5,864,035, January 26, 1999) discloses methods for preparing chlorins, bacteriochlorins and their derivatives. Pandey *et al.* (US 5,498,710, March 12, 1996) discloses methods for preparing alkyl ether analogs of benzoporphyrin derivatives. Dougherty *et al.* (US 5,190,966, March 2, 1993) discloses methods for preparing hematoporphyrin dimers. Pandey *et al.* (US 5,314,905, May 24, 1994) discloses methods for preparing pyropheophorbides. Pandey *et al.* (US 5,093,349, March 3, 1992) discloses methods for preparing methyl pheophorbide-a and monohydroxy deuteroporphyrins. Sessler *et al.* (US 5,733,903, March 31, 1998) discloses methods for preparing texaphyrines. Thus, methods of making photosensitizing compounds were known to those skilled in this art at the time of application.

Conjugating the Photosensitizer to the Binding Pair

The Examiner alleges that the specification does not teach how to use any claimed method because it is alleged that there is insufficient guidance as to how to bind a photosensitizing compound to the first member of a binding pair. The instant claims are directed to a method using a conjugate that includes a photosensitizing compound conjugated to a targeting moiety to treat neovascular disease of the eye. The techniques to conjugate a targeting moiety to a photosensitizing compound are well known to those of ordinary skill in this art and are specifically disclosed in the specification. For example, the specification teaches at paragraph [045] that:

> **[045]** The technique of constructing bispecific antibodies, the techniques and methods of linking photosensitizers to targeting agents, and the techniques of producing targeted liposomes are well known in the art. For example, useful reviews of such techniques are provided by Yatvin *et al.*, U.S. Patent No. 5,827,819 (1998) and Jansen, *et al.*, U.S. Patent No. 5,869,457 (1999).

The teachings of Yatvin *et al.* and Jansen *et al.* are incorporated in their entirety by reference in the instant application. Further, Rakestraw *et al.* teaches conjugating a chlorin via covalent bonds to monoclonal antibodies (Rakestraw *et al.*, *Proc. Nat. Acad. Sci. USA 87*: 4217-4221 (1990). Sessler *et al.* (U.S.

5,994,535 (1999)) teaches conjugating texaphyrin to antibodies, proteins and site-specific transport molecules. Sternberg *et al.* (*Tetrahedron 54*: 4151-4202 (1998)) teaches conjugating porphyrins to biomolecules including antibodies, steroids, sugars, and polynucleotides. Fritzberg *et al.* (U.S. 5,976,535 (1999)) teaches conjugating cytotoxic agents to one member of a ligand/anti-ligand binding pair, and teaches conjugation to a receptor, an oligonucleotide, an enzymatic substrate or other binding site present on or in the target cell population. Richter *et al.* (U.S. Patent No. 5,945,439 (1999)) teaches conjugating benzoporphyrin derivatives to specific ligands reactive with a target, such as receptor-specific ligands. It is further submitted that conjugating binding pairs to photosensitizing compounds was also known to those of skill in the art at the time the application was filed (for example, see Fritzberg *et al.*, U.S. 5,976,535 (1999); Davalian *et al.*, U.S. 5,616,719 (1997); and Pease *et al.*, U.S. 5,618,732 (1997)).

A variety of coupling agents, including cross-linking agents, can be used for covalent conjugation. Examples of cross-linking agents include N,N'-dicyclo-hexylcarbodiimide (DCC), N-succinimidyl-S-acetyl-thioacetate (SATA), N-succinimidyl-3-(2-pyridyldithio)propionate (SPDP) and *o*-phenylene-dimaleimide (*o*-PDM). See, *e.g.*, Karpovsky *et al. J. Exp. Med. 160*: 1686 (1984); and Liu, MA *et al.*, *Proc. Natl. Acad. Sci. USA 82*: 8648 (1985). Other methods include those described by Brennan *et al.*, *Science 229*: 81-83 (1985) and Glennie *et al.*, *J. Immunol. 139*: 2367-2375 (1987). A number of coupling agents and methods of use, are described in the Pierce Chemical Co. catalog, pages O-90 to O-110 (1995). Thus, there is extensive teachings in the art of conjugating compounds such as photosensitizing agents to ligands and receptors. It is respectfully submitted that it would not require undue experimentation to bind a photosensitizing compound to a targeting moiety.

Therefore, in light of the high level of skill in the art, and in light of the extensive teachings in the art of conjugating compounds such as ligands and receptors to photosensitizing agents, and the teachings of the specification, it is

respectfully submitted that it would not require undue experimentation to make a conjugate that includes a photosensitizing compound conjugated to a targeting moiety.

Alleged Insufficient Guidance as to "Other Agent"

The Examiner alleges that there is insufficient guidance as to which "other agent" mentioned in paragraph [039] that absorbs light in a range of 500nm-1100nm would be useful in the claimed method without an undue amount of experimentation. Applicant respectfully disagrees. The claims are directed to methods using a conjugate that includes a photosensitizing compound. The specification and the art at the time of application teaches that photosensitizing compounds share a number of characteristics. For example, a photosensitizing compound is preferentially taken up and selectively retained by hyperproliferative cells compared to normal cells (Kessel *et al.*, *Photochem Photobiology 58(2)*:200-203 (1993), page 200, first paragraph; Dougherty, *Seminars in Surgical Oncology 2*:24-37 (1986), page 24, first paragraph; and Pandey *et al.*, *J Molecular Recognition 9*: 118-122 (1996), page 118, first paragraph). Subsequent irradiation of the photosensitizing compound causes a photochemical reaction that is believed to generate chemically disruptive species, such as singlet oxygen, which disrupt or destroy the cell through reaction with cellular components or nuclear membranes (Weinstein *et al.*, U.S. Patent 4,753,958, col. 3, lines 9-38). Preferably, the chemical compound is nontoxic to the subject to which it is administered or is capable of being formulated in a nontoxic composition and the chemical compound in its photodegraded form also is nontoxic (see, *e.g.* paragraph [036] of the instant application). The specification directs the skilled artisan to a comprehensive listing of photosensitive chemicals may be found in Kreimer-Birnbaum, Sem. Hematol. 26:157-73, 1989 (see, *e.g.* paragraph [036]). A certain amount of experimentation is permissible as long as it is not undue. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. Applicant respectfully submits that routine testing can be used to determine whether a compound generates chemically disruptive species upon

exposure to light in the range of 500nm-1100nm, for example, or to determine whether it is toxic or non-toxic in its native and photodegraded state. Routine testing also can be used to determine whether a compound is preferentially taken up and selectively retained by hyperproliferative cells compared to normal cells. Thus, the amount of experimentation required to determine whether a compound that absorbs light in the range of 500nm-1100nm is a potential photosensitizing agent as instantly claimed is not undue.

Structure and Function of the Binding Pair

The Examiner alleges that the specification provides insufficient guidance as to the structure and function of the one member of the binding pair, such as a receptor, antigen, ligand or antibody, to which the targeted photosensitizing compound is bound. Applicant respectfully submits that in the embodiment that includes as a targeting moiety a binding pair, the targeting moiety is one member of a binding pair selected from the group consisting of a receptor present on abnormal endothelium; a ligand bindable to a receptor present on abnormal endothelium; an antigen present on abnormal endothelium; and an antibody bindable to an antigen present on abnormal endothelium (see claim 11). Applicant respectfully submits that the exact structure of the binding pair is not relevant to patentability.

Notwithstanding this, the specification provides as specific examples of binding pairs a bindable fragment of the L19 antibody to the ED-B of fibronectin and the ED-B of fibronectin (paragraph [054]), VEGF and VEGF receptor (paragraphs [058] and [059]), integrin $\alpha v\beta 3$ and anti-integrin $\alpha v\beta 3$ antibody (paragraph [061]), and carcinoembryonic antigen (CEA) and anti-CEA antibody (paragraph [063]).

It is respectfully submitted that receptors present on abnormal endothelium and ligands bindable to these receptors, and antigens present on abnormal endothelium and antibodies bindable to these antigens were well known to those skilled in the art at the time the application was filed. For example, Boulton *et al.* (Br. J Ophthalmol 82: 561-568 (1998)) discloses increased occurrence of VEGF

levels and VEGF receptors in patients with diabetic retinopathy and using anti-VEGF antibodies for immunostaining. Prewett *et al.* (Cancer Research 59: 5209-5218 (1999) discloses Flk-1 as a surface receptor expressed on endothelial cells associated with tumor angiogenesis and using anti-Flk-1 antibodies in the treatment of angiogenesis-dependent tumors. Thorpe *et al.* (U.S. Patent 5,877,279) teaches that blood vessels of vascularized tumors present a number of surface-expressed components and cell surface receptors and antibodies directed thereto, including endoglin (TEC-4 and TEC-11 antibodies), a TGFβ receptor, E- and P-selectins, PSMA, a VEGF/VPF receptor, an FGF receptor, a TIE, an $\alpha_v\beta_3$ integrin, pleiotropin, endosialin, MHC Class II proteins and aminophospholipids.

Additional endothelial receptors known at the time the application was filed include, among others, the extra-domain B (ED-B) of fibronectin (Birchler *et al.*, *Nature Biotech.* 17:984 (1999)); endothelial-leukocyte adhesion molecule (ELAM-1), vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), the agent for leukocyte adhesion molecule-1 (LAM-1 agent), and HLA-DR, HLA-DP or HLA-DQ (Thorpe, U.S. Patent No. 5,855,866 (1999); and the selectins, including L-Selectin (Rao *et al.*, U.S. Patent No. 5,624,909 (1997)).

The "function" of the binding pair directed to antigens, receptors or ligands on abnormal endothelium is to allow selective binding or targeting of the photosensitizing compound to specific receptors and/or antigens present on abnormal endothelium or to specific ligands and/or antibodies which are themselves bindable to endothelial receptors and antigens (see paragraphs [014] and [032]). The specification teaches a number of such binding pairs, including a binding pair that includes a ligand bindable to a receptor present on abnormal endothelium and a receptor present on abnormal endothelium, and teaches as another binding pair an antibody bindable to antigen present on abnormal endothelium and an antigen present on abnormal endothelium (see paragraph [020]). Using binding pairs for targeting purposes was well known in this art at the time of filing this application (*e.g.*, see Thorpe *et al.* (U.S. Patent 5,877,279).

Therefore, in light of the high level of skill in the art, and in light of the extensive teachings in the art on binding pairs and on conjugating compounds to binding pairs, and the teachings of the specification, which includes generic and specific examples of binding pairs, and provides working examples of exemplary binding pairs conjugated to photosensitizing compounds, and in light of the extensive teachings in the art on antigens, receptors or ligands on abnormal endothelium, and the teachings of the specification, which includes generic and specific examples of binding pairs, and that provides working examples of exemplary targeting moieties on abnormal endothelium, it is respectfully submitted that it would not require undue experimentation to select a binding pair to which a photosensitizing compound can be conjugated to provide specific targeting to abnormal endothelium.

Antibody Binding Specificity

The Examiner alleges that, because the specific antigen, receptor or ligand is not disclosed in the specification, the binding specificity of the antibody is questionable, and alleges that the method is not enabled because without knowing the antibody binding specificity it is questionable whether the targeted photosensitizing compound would bind specifically to the undisclosed antigen on the abnormal endothelium. Applicant respectfully submits that none of the pending claims is directed to any specific antibody. Claim 11 is directed to a method of treating neovascular disease of the eye that includes using a conjugate that includes a photosensitizer compound conjugated to one member of a binding pair, where the binding pair is selected, in one embodiment, to include an antibody bindable to endothelial receptors and/or antigens. Thus, the overall structure of the antibody and its exact binding specificity is not pertinent to patentability. The antibody need only demonstrate the ability to combine specifically or have a high degree of affinity for abnormal endothelium when compared to its reactivity toward non-target tissue, so that the antibody can serve as a targeting moiety by which a photosensitizing compound conjugated to the antibody can selectively bind to abnormal endothelium.

The specification teaches that the antibody is **selected** to be bindable to endothelial receptors and antigens ([014]), and provides as examples antibody elicited to an antigenic determinant on abnormal endothelium, such as the extra domain B of fibronectin (paragraph [021]) and $\alpha v\beta 3$ integrins (paragraph [061]) or to antigen associated with choroidal tumor, such as carcinoembryonic antigen (paragraph [063]). Methods of making antibodies with specificity to abnormal endothelium were known at the time the application was filed (see Thorpe, U.S. Patent No. 5,855,866 (1999)).

Therefore, in light of the high level of skill in the art, and in light of the extensive teachings in the art on antibodies having specificity to abnormal endothelium, and the teachings of the specification, which includes generic and specific examples of antibodies having specificity to abnormal endothelium, and which provides working examples of exemplary antibodies, it is respectfully submitted that it would not require undue experimentation to select an antibody having specificity to abnormal endothelium to which a photosensitizing compound can be conjugated to allow targeting of the photosensitizing compound to abnormal endothelium.

Intensity of Light

The Examiner alleges that the specification provides insufficient guidance as to the intensity of light used for the claimed method "given the infinite number of undisclosed targeted photosensitizing compounds." Applicant respectfully submits that the specification teaches the requisite properties for photodynamic therapy. The specification teaches, for example, using an intensity of light substantially less that 500 mW/cm^2, and that since the total fluence or amount of energy of the light in Joules is divided by the duration of total exposure time in seconds, the longer the amount of time the target is exposed to the irradiation, the greater the amount of total energy or fluence may be used without increasing the amount of the intensity of the light used (see paragraph [050]. For example, the specification discloses using a low power light source emitting at 690 nm and having an intensity of 250 mW/cm^2 to irradiate a subject for approximately 1 hour

over the course of one or more sessions to provide a total fluence of 900 J/cm^2 (see, e.g. paragraph [066]. The specification also discloses irradiating a subject in one or more sessions for a total period of 10 minutes with light having an intensity of 400 mW/cm^2 and a wavelength of 690 nm, resulting in a total fluence of 240 Joules/cm^2 (see, e.g., paragraph [055]). Thus, the specification teaches that the claimed subject matter uses a combination of a selected intensity of light, for example, less than 500 mW/cm^2, administered over a period of time selected to achieve a total fluence of irradiation that is sufficiently high to activate the photosensitizing agent, as applicable, with a concomitant reduction in the intensity of light required for activation (see paragraphs [053] and [057]). The specification also teaches other parameters of the disclosed photodynamic method. For example, the specification teaches that the photosensitizing compounds have a light absorbance in a range of 500 to 1100 nm (paragraph [036]) and that the light for irradiating the target tissue includes a wavelength corresponding with the characteristic light absorption wavelength of the photosensitizing agent (see, *e.g.*, [049]). The specification teaches that the duration of illumination will be determined empirically but is preferably a total or cumulative period of time between 4 minutes and 148 hours (see, *e.g.*, paragraph [048]). The specification also teaches that the total fluence of the light is between 30 Joules and about 25,000 Joules (see, *e.g.*, paragraph [049]). Therefore, in light of the teachings of the specification and what is known to those skilled in this art, the specification provides sufficient guidance for selecting the intensity of the light to be used in the claimed method.

Alleged Lack of Upper Limit of Illumination

The Examiner alleges that even if the photosensitizing compound is enabled, the light source, the combination of the intensity of light used for the step of illumination and the duration of illumination to arrive at the total fluence "are critical for the claimed method" and that "given the lack of an upper limit for the duration of illumination, it is not clear if the claimed method as written is effective for treating neovascular disease without impairing or destroying other

tissues." Applicant respectfully disagrees. The specification teaches at paragraphs [013] - [016] that:

> The present invention describes methods to treat neovascular disease of the eye based on the precise targeting of photosensitive compounds to target tissue and the activation of these targeted photosensitizer compounds by subsequently administering to the subject non-coherent (non-laser) or coherent (laser) light of a relatively low fluence rate over a prolonged period of time.
>
> The present invention further discloses the selective binding of the photosensitizing agent to specific receptors and/or antigens present on abnormal endothelium or to specific ligands and/or antibodies which are themselves bindable to endothelial receptors and antigens. This targeting scheme decreases the amount of sensitizing drug required for effective therapy, which in turn reduces the fluence rate or light irradiation needed for effective photoactivation. As a result, the disclosed method achieves maximal dosage to abnormal endothelium with minimal side effects or collateral tissue damage.
>
> Additionally, the present disclosure teaches the unexpected use of a low power non-coherent light source utilized for longer than about 4 minutes. This teaches away from the use of a high powered, brief exposure using laser light, results in fuller, more efficient activation of the bound photosensitizers, and enables a high therapeutic index using a low dose drug. Moreover, a low power non-coherent light source is relatively inexpensive and simpler to use. Finally, because the present invention teaches photoactivation with a non-coherent, broadband light source, different types of photosensitizers can be activated with a single light source.
>
> Due to the highly specific nature of the photosensitizer uptake, excess light or light falling on nonpathologic areas causes no unwanted photoactivation. Therefore, a region of the retina or macular with diffuse abnormalities can be safely treated without damaging intervening normal eye structures. In addition, eye movement by the patient during treatment, which can result in the further exposure to light of normal eye structures, is harmless. Thus, the use of highly targeted photosensitizers allows the delivery of light in a diffuse fashion and over a prolonged illumination period. In fact, one embodiment of the invention is the use of ambient light to activate the photosensitized neovascular tissue.

Thus, the specification discloses that selection of a combination of a low intensity light and a prolonged duration of irradiation to activate the photosensitizer reduces

the potential for damage to non-target tissue exposed to the irradiation. Contrary to the Examiner's assertion, there is no "lack of an upper limit for the duration of illumination," because an upper limit is not required for the claimed method. The specification teaches, at paragraph [050], that the duration of illumination depends on the intensity of the light chosen so that the desired total fluence is achieved:

> The intensity or power of the light used is measured in watts, with each Joule equal to one watt-sec. Therefore, the intensity of the light used for irradiating in the present invention may be substantially less than 500 mW/cm^2. Since the total fluence or amount of energy of the light in Joules is divided by the duration of total exposure time in seconds, the longer the amount of time the target is exposed to the irradiation, the greater the amount of total energy or fluence may be used without increasing the amount of the intensity of the light used. The present invention employs an amount of total fluence of irradiation that is sufficiently high to activate the photosensitizing agent, as applicable, with a concomitant reduction in the intensity of light and collateral or non-target specific tissue damage.

Thus, an extended duration of irradiation is achieved by a concomitant reduction in the intensity of the light used. Hence, one skilled in this art, in light of the teachings of the specification, would be able to select a combination of light intensity and a duration of irradiation to activate the photosensitizer while minimizing any damage to non-target tissue.

CONCLUSION

In light of the scope of the claims, the teachings in the specification, the presence of specific working examples in the specification, the high level of skill of those in this art, and the knowledge of those of skill in this art, it would not require undue experimentation for a person of skill in the art to select a targeting moiety and a photosensitizing compound to practice a method of photodynamic therapy to treat neovascular disease of the eye as claimed; or to select as a targeting moiety one member of a binding pair that includes an antibody, an antigen, a ligand, or a receptor specific for abnormal endothelium to practice a method of photodynamic therapy to treat neovascular disease of the eye as claimed. Therefore, the specification is enabling for making and using the full

scope of the claimed subject matter. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

REBUTTAL TO EXAMINER'S ARGUMENTS

Protein Structure

The Examiner alleges that without the guidance as to the structure of the protein such as the antigen, the receptor, or the ligand, it is allegedly unpredictable which undisclosed antigen, receptor and ligand would be effective for targeting any photosensitizing compound to abnormal endothelium. Applicant respectfully disagrees. As discussed above, none of claims 1-6, 11-12, 16-24, 36 or 38-41 are directed to any specific antigen, receptor or ligand. Thus, the overall structure of the antigen, receptor or ligand is not relevant to patentability. As discussed above, the literature discloses and one skilled in this art is familiar with a number or different antigens, receptors and ligands associated with abnormal endothelium. Further, the applicant submits that the claimed antigens, receptors or ligands are not restricted to protein. It is well known to those skilled in this art that antigens and ligands are not limited to proteins, but include carbohydrates, such as the blood group antigens (see Janeway *et al.*, Immunobiology, 3rd ed., 1997, page 2.12), glycans, lipo-polysaccharides or peptides (Janeway *et al.*, pages 3:8, 3:9 and 9:11).

It is respectfully submitted that no evidence is provided to support the Examiner's position that "without the guidance as to the structure of the protein such as the antigen, the receptor, or the ligand it is allegedly unpredictable which undisclosed antigen, receptor and ligand would be effective for targeting any photosensitizing compound to abnormal endothelium." No reference is provided to show that antigens, receptors and ligands of abnormal endothelium are only protein. The Examiner is reminded that MPEP 2144.03 states:

> The Examiner may take official notice of facts outside of the record which are capable of instant and unquestionable demonstration as being "well- known" in the art. In re Ahlert, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970). . . ..

The facts of which the Examiner is taking notice are conclusory and are not capable of instant and unquestionable demonstration as being "well-known" in the art. MPEP 2144.03 continues:

> If justified, the examiner should not be obliged to spend time to produce documentary proof. If the knowledge is of such notorious character that official notice can be taken, it is sufficient so to state. In re Malcolm, 129 F.2d 529, 54 USPQ 235 (CCPA 1942). If the applicant traverses such an assertion the examiner should cite a reference in support of his or her position.

Hence, if this position is maintained, the Examiner must provide a reference supporting this position.

Antibodies Directed to Proteins

The Examiner alleges that antibody binding specificity differs depending on how the antibodies are elicited. The Examiner cites to Kuby *et al.* for the proposition that antibody binding specificity depends on whether a full-length polypeptide or a peptide fragment is used as the immunogen to elicit the antibody. The applicant submits that while the structure of an immunogen may determine specificity during antibody formation (such as using a peptide versus a full-length polypeptide as alleged by the Examiner), antibodies raised against a given antigen can cross-react with a partially related antigen which bears one or more identical or similar immunodeterminants (Roitt, *Essential Immunology*, pages 14-15, 1984). It is respectfully submitted that the instant claims are not directed to generation of antibodies. The specification teaches selecting an antibody that demonstrates the ability to combine specifically or that has a high degree of affinity for abnormal endothelium (see paragraph [021]), so that a photosensitizing compound which is conjugated to a targeting moiety such as an antibody can selectively bind to abnormal endothelium. Such antibodies are known to those skilled in this art (for example, see Thorpe, U.S. Patent No. 5,855,866 (1999)).

REJECTION OF CLAIMS 1-6, 11-12, 16-24 and 36 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-6, 11-12, 16-24 and 36 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter that was not described in the

specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed subject matter. The Examiner alleges that the specification only provides a written description for a method to treat neovascular disease of the eye using verteporfin conjugated to L19 antibody that binds to the ED-B domain of fibronectin, and benzoporphyrin conjugated to VEGF, that selectively binds to abnormal endothelium that lines or composes neovascular tissue. The Examiner contends that there is insufficient written description about the structure and function of any photosensitizing compound, the binding specificity of any antibody, or the targeted antigen. The Examiner alleges that the specification discloses only one ligand (the ED-B domain of fibronectin), one specific binding pair (VEGF that binds to the VEGF receptor), one antibody (antibody to the ED-B domain of fibronectin), and only two photosensitizing compounds (verteporfin and benzoporphyrin), and thus alleges that the specification fails to provide a representative number of species to describe the genus.

This rejection is respectfully traversed.

RELEVANT LAW

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject mater at the time of filing of the application *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description has been stated as:

> [d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound [claimed embodiment] *Vas-Cath, Inc. v. Mahurkar*, at 1115, quoting *In re Ruschig*, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, s/he was in possession of the invention, *i.e.*, whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985). The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 265 (CCPA 1976).

THE CLAIMS

The claims are discussed above.

ANALYSIS

The Examiner alleges that, with the exception of the specific ligands recited in claim 13, the specification discloses as species of the claimed genera only one ligand (ED-B of fibronectin), one specific binding pair (VEGF that binds to a VEGF receptor), one antibody (antibody to the ED-B of fibronectin) and only two photosensitizing compounds (verteporfin and benzoporphyrin), and alleges that such a disclosure is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genera.

First, it is noted that the original claims are part of the specification; hence, the genus including the specific ligands of claim 13 is disclosed in the specification. Second, applying the guidelines for a written description analysis of claims directed to a genus reveals that the written description requirement is satisfied. The analysis for compliance with the written description requirement where claims are directed to a genus is as follows:

a) does the art indicate substantial variation among the species within the genus?

b) are there a representative number of examples explicitly or implicitly disclosed in the application as determined by assessing whether the skilled artisan would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed bythe members of the genus in view of the disclosed species?

The claimed "genera"

As discussed above and below, claim 1 is directed to a method of photodynamic therapy to treat neovascular disease of the eye that includes administering a conjugate that includes a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium that lines or composes neovasculature tissue. Thus, "photosensitizing compound" represents a genus. Claim 11 and its dependent claims are directed to a method of claim 1 where the targeting moiety is a first member of a binding pair, and thus "binding pair" represents a genus. The "genus" encompasses the exemplified species and other species that are similar in function to the exemplified species.

Photosensitizing Compound

a) The claims are directed to methods of photodynamic therapy that include a photosensitizing compound that, when contacted by radiation, absorbs light, which results in impairment or destruction of the target cells (see paragraph [036]). As discussed above, there are many photosensitizing compounds known to the skilled artisan. The specification teaches that the claimed conjugates include photosensitizing compounds that possess common elements. For example, the specification teaches that the photosensitizing compound is nontoxic

to the subject prior to irradiation or in its photodegraded form, and absorbs light in a range of 500-1100 nm (paragraph [036]), whereby the photosensitizing compound is activated and generates singlet oxygen and other reactive species that have biological effects resulting in damage to the endothelial membranes and ultimately to clotting the neovasculature (see paragraph [005]). Thus, there is no substantial variation among the species within the genus.

b) The specification provides a representative number of examples explicitly (17 by compound family, including porphyrins, purpurin, chlorins, bacteriochlorophylls, phthalocyanines, merocyanines, psoralens, benzoporphyrin derivatives, porfimer sodium, δ-aminolevulinic acid, pyropheophorbides, texaphyrins, verteporfin, indocyanine green, methylene blue, and toluidine blue and two by specific tradename (PHOTOPHRIN® and FOSCAN®) and implicitly by defining the properties requisite for activity in photodynamic therapy. The applicant provides specific working examples that include three different photosensitizing compounds (verteporfin [054], benzoporphyrin [058], and texaphyrin [061]). Accordingly, applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species so that the skilled artisan would recognize that applicant "had possession" of the genus as claimed.

Binding Pair

The subject matter of claim 11 and its dependent claims is directed to a method of photodynamic therapy to treat neovascular disease of the eye that includes a conjugate that includes a photosensitizing compound conjugated to a binding pair that allows the selective binding of the photosensitizing compound to specific receptors and/or antigens present on abnormal endothelium or to specific ligands and/or antibodies which are themselves bindable to endothelial receptors and antigens (see paragraph [032]).

One member of the binding pair is conjugated to the photosensitizing compound and combines with its counterpart to target the photosensitizing compound. The binding pair can include as one member of the binding pair a

receptor present on abnormal endothelium, a ligand bindable to receptor present on abnormal endothelium, an antigen present on abnormal endothelium, an antibody bindable to antigen present on abnormal endothelium, and an antibody bindable to a receptor present on abnormal endothelium.

a) The specification teaches that the ligand can be any molecule or compound that binds specifically to abnormal endothelium, for example upregulated receptors or receptors on abnormal blood vessel walls (see paragraph [042]). Thus, one of skill in the art would recognize one common element of the claimed receptors is that they are mainly or only found on the abnormal endothelium. For example, as discussed above, at the time the application was filed, many endothelial receptors were known, including VEGF receptors, $\alpha v\beta 3$ integrins, the extra-domain B (ED-B) of fibronectin, endothelial-leukocyte adhesion molecule (ELAM-1), vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and the selectins. Similarly, the ligands that bind to these receptors also were known, such as VEGF for VEGF receptors, fibrinogen and fibronectin for $\alpha v\beta 3$ integrins, LFA-1 for ICAM-1 and VLA-4 for VCAM-1. The specification also teaches that the binding pair can include antibodies that are bindable to endothelial receptors or to endothelial antigens (see paragraph [032]). Thus, one of skill in the art would recognize as one common element of the claimed antibodies their specificity or high degree of affinity for ligands that bind to upregulated receptors on blood vessels or receptors that are mainly or only found on abnormal endothelium. Thus, there are common conserved elements among the receptors and/or antigens and/or ligands and/or antibodies of the binding pair capable of binding to target endothelium.

b) The specification provides a representative number of examples of receptors, antigens, ligands and antibodies of the binding pair explicitly (including VEGF, VEGF receptor, $\alpha v\beta 3$ integrin receptor, CEA antigen, antibody to the extra-domain B of fibronectin, such as L19, antibody to $\alpha v\beta 3$, such as LM609, antibody to CEA, and bispecific antibody construct that is a combination of ligand and receptor (see paragraphs [021], [043], [044] and [061]) and implicitly (such as

antibodies and antibody fragments that bind to abnormal vascular endothelial receptors, and antibodies and antibody fragments that bind to upregulated vascular endothelial receptors). The specification defines the properties requisite for activity (binding to an upregulated endothelial receptor or an endothelial receptor found on an abnormal blood vessel wall). The applicant provides specific working examples that include four different ligands (ED-B of fibronectin [054], VEGF [058], $\alpha v\beta 3$ integrin [061], and carcinoembryonic antigen [063]) and 2 receptors (VEGF receptor [059] and $\alpha v\beta 3$ integrin [061]). Accordingly, applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species so that the skilled artisan would recognize that applicant "had possession" of the genus as claimed.

REJECTION OF CLAIMS 1-9, 11-12, 16-24, 36 and 38-41 UNDER 35 U.S.C. §112, FIRST PARAGRAPH - ALLEGED NEW MATTER

Claims 1-9, 11-12, 16-24, 36 and 38-41 are rejected under 35 U.S.C. 112, first paragraph, allegedly for containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed subject matter. The Examiner alleges that the insertion of the recitation "total fluence of irradiation" into claim 1 in the previous Response represents a departure from the specification and claims as originally filed.

This rejection is respectfully traversed.

ANALYSIS

It is respectfully submitted that, at the time of application, applicant appreciated and was in possession of a method of photodynamic therapy that includes as a step selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular target tissue is destroyed and the non-target tissue through which the light passes remains undamaged, as instantly claimed.

The specification provides specific basis for the recitation "total fluence of irradiation" at paragraph [050]:

> The intensity or power of the light used is measured in watts, with each Joule equal to one watt-sec. Therefore, the intensity of the light used for irradiating in the present invention may be substantially less than 500 mW/cm^2. Since the total fluence or amount of energy of the light in Joules is divided by the duration of total exposure time in seconds, the longer the amount of time the target is exposed to the irradiation, the greater the amount of total energy or fluence may be used without increasing the amount of the intensity of the light used. The present invention employs an amount of **total fluence of irradiation** that is sufficiently high to activate the photosensitizing agent, as applicable, with a concomitant reduction in the intensity of light and collateral or non-target specific tissue damage. (emphasis added)

Thus, the recitation "total fluence of irradiation" has basis in the original disclosure and complies with the written description requirement of 35 U.S.C. §112. Hence, the recitation "total fluence of irradiation" does not introduce new matter because the specification as filed discloses this embodiment of the claimed subject matter. Therefore, because the recitation "total fluence of irradiation" is subject matter that is supported by or conforms to the disclosure of the application as filed, the rejection under 35 U.S.C. §112, first paragraph should be withdrawn.

THE REJECTION OF CLAIMS 1, 3, 4, 6, 18-21, 36 and 41 UNDER 35 U.S.C. §102(b)

Claims 1, 3, 4, 6, 18-21, 36 and 41 are rejected under 35 U.S.C. § 102 as anticipated by Strong *et al.* (U.S. Patent No. 5,756,541) because Strong *et al.* allegedly discloses a method to treat neovascular disease of the eye such as age-related macular degeneration that includes administering a photosensitizing compound such as a chlorin and green porphyrin coupled to a specific binding ligand such as an antibody that binds to the target ocular tissue.

This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), *cert. denied*, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). It is incumbent on the Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention.

THE CLAIMS

Claim 1 is directed to a method to treat neovascular disease of the eye that includes administering a conjugate that includes a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium that lines or composes neovascular target tissue in the eye; allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue; and illuminating the neovascular target tissue with light using a non-coherent light source including a wavelength corresponding at least in part with the characteristic light absorption wavelength of the photosensitizing compound for a period of time sufficient to activate the photosensitizing compound, where a combination of an intensity of light used for the step of illuminating and a duration of illumination is selected to produce a total fluence of irradiation such that the neovascular target tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Claims 3, 4, 6, 18-21, 36 and 41 ultimately depend from claim 1 and are directed to various embodiments thereof.

Disclosure of Strong *et al.*

Strong *et al.* discloses a photodynamic therapy of the eye to reduce unwanted neovasculature, especially neovasculature of the choroid (col. 2, lines 1-3). Strong *et al.* discloses that its green porphyrins strongly interact with lipoproteins (col. 3, lines 53-56). Strong *et al.* discloses coupling the photo-sensitizer to a target-specific ligand such as an antibody or an immunologically active fragment or formulating in a liposome (col. 4, lines 8-16). Strong *et al.* discloses that fluence during the irradiating treatment varies from about 50-200 J/cm^2 (col. 4, lines 56-59), and that irradiance varies from about 150-900 mW/cm^2 (col. 4, lines 60-64). Strong *et al.* discloses waiting a "suitable time period to permit an effective concentration of the compound to accumulate in the desired region of the eye" (col. 2, lines 27-29) and to "localize in the eye" (co. 2, line 10). Strong *et al.* discloses administering light from a coherent argon dye laser (col. 5, lines 45-51). Strong *et al.* discloses that its treatment results in deleterious effects of the tissue immediately surrounding the activated photosensitizer (col. 2, lines 31-33), such as mild retinal whitening in some cases (col. 5, lines 10-13).

Differences between the claimed subject matter and the disclosure of Strong *et al.*

Strong *et al.* does not disclose a method to treat neovascular disease of the eye that includes allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue. Strong *et al.* discloses waiting a period of time to permit an effective concentration of the compound to localize or accumulate in the desired region of the eye. Strong *et al.* does not disclose clearance of the photosensitizer from non-target tissue, nor does the reference disclose waiting any period of time after administration of the photosensitizer prior to irradiation to allow any photosensitizer that is not specifically bound to the target tissue to clear from healthy non-target tissue.

Strong *et al.* does not disclose selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to achieve target tissue destruction without damage to non-target tissue. Instead, Strong *et*

al. discloses that its method results in deleterious effects of the tissue immediately surrounding the activated photosensitizer, making no distinction between target and non-target tissue, and discloses that mild retina whitening occurs (see, *e.g.*, col. 2, lines 31-33 and col. 5, lines 10-13). Hence, Strong *et al.* does not disclose selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Thus, Strong *et al.* does not disclose every element of claim 1. Because Strong *et al.* does not disclose every element of claim 1, Strong *et al.* does not anticipate claim 1. Because claims 3, 4, 6, 18-21, 36 and 41 depend from claim 1, Strong *et al.* does not anticipate any of the pending claims. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

Rebuttal to Examiner's Arguments

Claims 19-21

The Examiner alleges that Strong *et al.* discloses illuminating the photoactive agent for about 1 minute to about 2 hours, and cites col. 5, lines 2-4 to support the allegation. The applicant respectfully disagrees. Strong *et al.* discloses that

> [t]he optimum time <u>following</u> photoactive agent administration **<u>until</u>** light treatment can also vary widely depending on the mode of administration, the form of administration and the specific ocular tissue being targeted. Typical times after administration of the photoactive agent range from about 1 minutes to about 2 hours, preferably about 5-30 minutes, and more preferably 10-25 minutes.

[emphasis added] (col. 4, line 65 through col. 5, line 4). The cited section discloses the interval between administration of the photoactive agent and the administration of light, and does NOT disclose a time for illumination as alleged by the Examiner.

REJECTION OF CLAIMS 1, 2, 11, 12 and 38-40 UNDER 35 U.S.C. §103(a)

Claims 1, 2, 11, 12 and 38-40 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Strong *et al.* (U.S. Patent No. 5,756,541) in view of Boulton *et al.* (*Br. J Opthalmol 82*: 561-568, 1998), Blaauwgeers *et al.* (*Am J Pathology 155(2)*: 421-428, 1999), Klyashchitsky *et al.* (*J of Controlled Release 29(1-2)*: 16-16, 1994) and Prewett *et al.* (*Cancer Res 59*: 5209-18, 1999) because although Strong *et al.* does not teach non-laser light (claim 2), or binding the photosensitizer to a first member of a binding pair (claim 11), or incorporation of a conjugate that includes a photosensitizing compound conjugated to a targeting moiety into a liposomal preparation (claim 12), Boulton *et al.*, Blaauwgeers *et al.*, Klyashchitsky *et al.* and Prewett *et al.* allegedly cure these defects.

This rejection is respectfully traversed.

RELEVANT LAW

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.*, 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall

victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

THE CLAIMS

The claims are discussed above.

Differences Between the Claims and the Teachings of the Cited References

Strong *et al.*

The teachings of Strong *et al.* are discussed above.

Boulton *et al.*

Boulton *et al.* teaches that VEGF was generally absent from normal retina and that staining of tissue using anti-VEGF antibody showed VEGF in most diabetic tissue, but that this was dependent on both the specificity of the antibody used and the category of the tissue (page 561, col. 1., lines 24-29). Boulton *et al.* teaches that some anti-VEGF antibodies also associated with extravascular components of the inner retina (page 561, col. 1, lines 33-35). The reference teaches that VEGF staining correlated with active neovascularization and that VEGF may play a role in diabetic retinopathy (page 566, col. 1, lines 48-56). Boulton *et al.* teaches laser photocoagulation (page 567, col. 1, lines 26-31).

Boulton *et al.* does not teach or suggest a conjugate that includes a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium. Boulton *et al.* does not disclose allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue. Boulton *et al.* does not disclose administering light from a non-coherent light source to activate the photosensitizing compound. Boulton *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Blaauwgeers *et al.*

Blaauwgeers *et al.* teaches that the retinal pigment epithelium monolayer is involved in the pathogenesis of choroidal neovascularization such as in age-related macular degeneration (page 421, col. 2, lines 13-16). Blaauwgeers *et al.* teaches that up-regulated basolateral VEGF secretion or loss of polarity of VEGF production may play a role in the pathogenesis of choroidal neovascularization (page 421, col. 2, lines 3-9). The reference teaches that defects in the retinal pigment epithelium monolayer could lead to misdirection of secreted VEGF and subsequent classical subretinal neovascularization (page 428, col. 1, lines 1-4).

Blaauwgeers *et al.* does not teach or suggest treating neovascular disease using a photosensitizing compound, nor does the reference teach or suggest a conjugate that includes a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium. Blaauwgeers *et al.* does not disclose allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue. Blaauwgeers *et al.* does not disclose administering light from a non-coherent light source to activate the photosensitizing compound. Blaauwgeers *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Klyashchitsky *et al.*

Klyashchitsky *et al.* teaches that photodynamic therapy is based on the ability of porphyrins and some other photosensitizers to accumulate preferentially in tumor cells and to generate singlet oxygen when activated by visible light (page 1, abstract). Klyashchitsky *et al.* teaches targeted photosensitizers using targeting moieties having high affinity to the tumor-associated antigen or receptor (page 2, col. 2, lines 21-26). Klyashchitsky *et al.* teaches that such targeting moieties include monoclonal antibodies, liposomes, low density lipoproteins and lectins (page 2, col. 1, lines 24-33).

Klyashchitsky *et al.* does not teach or suggest treating neovascular disease using a photosensitizing compound, nor does the reference teach or suggest a conjugate that includes a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium. Klyashchitsky *et al.* does not disclose allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue. Klyashchitsky *et al.* does not teach or suggest non-coherent light for illuminating neovascular tissue to activate a photosensitizing compound. Klyashchitsky *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Prewett *et al.*

Prewett *et al.* teaches that tumor angiogenesis is mediated by tumor-secreted growth factors that interact with their surface receptors expressed on endothelial cells, and that VEGF and the VEGF receptor play a role in vascular permeability and tumor angiogenesis (page 5209, col. 1, lines 1-5). Prewett *et al.* teaches that anti-VEGF receptor antibody treatment of tumors results in decreased microvessel density, tumor cell apoptosis, decreased tumor cell proliferation and extensive tumor necrosis (page 5209, col. 1, lines 23-29). The reference teaches that VEGF and VEGF receptors are implicated in angiogenesis that occurs in many human solid tumors (page 5209, col. 2, lines 25-27), and that blocking the VEGF receptor with anti-VEGF receptor antibodies inhibits angiogenesis (page 5214, col. 2, lines 9-12). Prewett *et al.* teaches that neutralizing soluble VEGF receptor or Flk-1/KDR kinase inhibitors inhibited angiogenesis and tumor growth (page 5209, col. 2, lines 33-37).

Prewett *et al.* does not teach or suggest treating neovascular disease using a photosensitizing compound, nor does the reference teach or suggest a conjugate that includes a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium. Prewett *et al.* does not disclose

allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue. Prewett *et al.* does not teach or suggest illuminating neovascular tissue to activate a photosensitizing compound, nor does the reference teach or suggest non-coherent light for such illumination. Prewett *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness because of the following.

The combination of teachings of Strong *et al.* with the teachings of Boulton *et al.*, Blaauwgeers *et al.*, Klyashchitsky *et al.* and Prewett *et al.* does not result in the instantly claimed methods.

Independent claim 1 and its dependent claims include as subject matter administering a therapeutically effective amount of a conjugate that includes a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium that lines or composes neovascular target tissue in the eye; allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue; and illuminating the neovascular target tissue with light using a non-coherent light source including a wavelength corresponding at least in part with the characteristic light absorption wavelength of the photosensitizing compound for a period of time sufficient to activate the photosensitizing compound, where a combination of an intensity of light used for the step of illuminating and a duration of illumination is selected to produce a total fluence of irradiation such that the neovascular target tissue is destroyed and the non-target tissue through which the light passes remains undamaged. As discussed above in the traverse under §102, Strong *et al.* does not teach or suggest allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue, nor selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to produce a total

fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Boulton *et al.* does not cure these defects. Boulton *et al.* does not teach or suggest treating neovascular disease using a photosensitizing compound, and thus Boulton *et al.* does not teach or suggest allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue, nor does the reference teach or suggest the parameters of the intensity or duration of light used for photodynamic therapy. Boulton *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Hence, even if, arguendo, Boulton *et al.* teaches that VEGF plays a role in neovascularization in diabetic retinopathy, the combination of the teachings of Strong *et al.* and Boulton *et al.* does not teach or suggest every element of claim 1 and its dependent claims.

Blaauwgeers *et al.* does not cure these defects. Blaauwgeers *et al.* does not teach or suggest treating neovascular disease using a photosensitizing compound. Blaauwgeers *et al.* does not teach or suggest allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue. The reference does not teach or suggest any intensity or duration of light to be used for photodynamic therapy, nor selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Thus, combining the teachings of Blaauwgeers *et al* with Strong *et al.* or with the combination of Strong *et al.* and Boulton *et al.* does not teach or suggest allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue. Combining the teachings of Blaauwgeers *et al* with Strong *et al.* or with the combination of Strong *et al.* and Boulton *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a

duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Hence, even if, arguendo, Blaauwgeers *et al.* teaches that the loss of polarity of VEGF production may play a role in the pathogenesis of choroidal neovascularization, the combination of the teachings of Blaauwgeers *et al.* with Strong *et al.* or with the combined teachings of Strong *et al.* and Boulton *et al.* does not teach or suggest every element of claim 1 and its dependent claims.

Klyashchitsky *et al.* does not cure these defects. Klyashchitsky *et al.* teaches targeting photosensitizers to tumors using monoclonal antibodies, liposomes, low density lipoproteins and lectins that have high affinity to a tumor-associated antigen or receptor. Klyashchitsky *et al.* does not teach or suggest allowing sufficient time to permit the non-specifically bound photosensitizer to clear from non-target tissue, nor any intensity or duration of light to be used for photodynamic therapy. Klyashchitsky *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Hence, even if, arguendo, Klyashchitsky *et al.* teaches targeted photosensitizers, combining the teachings of Klyashchitsky *et al.* with the teachings of Strong *et al.*, or the combined teachings of Strong *et al.* and Boulton *et al.*, or the combined teachings of Strong *et al.* and Boulton *et al.* and Blaauwgeers *et al.* fails to teach or suggest every element of claim 1 and its dependent claims.

Prewett *et al.* does not cure these defects. Prewett *et al.* teaches that VEGF and the VEGF receptor play a role in vascular permeability and tumor angiogenesis and that anti-VEGF receptor antibody treatment of tumors results in decreased microvessel density and tumor necrosis. Prewett *et al.* does not teach or suggest treating neovascular disease using a photosensitizing compound or a conjugate that includes a photosensitizing compound, and thus Prewett *et al.* does

not teach or suggest allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue. Prewett *et al.* does not teach or suggest any intensity or duration of light to be used for photodynamic therapy. Prewett *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Hence, even if, arguendo, Prewett *et al.* teaches that blocking the VEGF receptor with anti-VEGF receptor antibodies inhibits angiogenesis, combining the teachings of Prewett *et al.* with the teachings of Strong *et al.*, or with the combined teachings of Strong *et al.* and Boulton *et al.*, or with the combined teachings of Strong *et al.*, Boulton *et al.* and Blaauwgeers *et al.*, or with the combined teachings of Strong *et al.*, Boulton *et al.*, Blaauwgeers *et al.* and Klyashchitsky *et al.* fails to teach or suggest every element of claim 1.

Thus, the combination of the teachings of Strong *et al.* and Boulton *et al.* and Blaauwgeers *et al.* and Klyashchitsky *et al.* and Prewett *et al.* does not result in the subject matter of claims 1, 2, 11 and 12. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

REJECTION OF CLAIMS 1, 16 and 17 UNDER 35 U.S.C. §103(a)

Claims 1, 16 and 17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Strong *et al.* (U.S. Patent No. 5,756,541) in view of Thorpe *et al.* (U.S. Patent No. 6,051,230) because Strong *et al.* allegedly teaches every element of the claimed subject matter except a targeted photosensitizing compound that is bound to a bi-specific antibody, but Thorpe *et al.* allegedly cures this defect. The Examiner contends that Thorpe *et al.* teaches various antibodies to VEGF and methods of making bi-specific antibodies, and that bi-specific antibodies carrying diagnostic or therapeutic agents are targeted to the vasculature through recognition of VEGF or other receptors on endothelial cells. The Examiner contends that it would have been obvious to substitute the bi-

specific antibodies of Thorpe *et al.* for the antibody taught in Strong *et al.* for targeting the photosensitive compound to neovasculature tissue in the eye.

This rejection is respectfully traversed.

RELEVANT LAW

The relevant law is discussed above.

THE CLAIMS

The claims are discussed above.

Differences Between the Claims and the Teachings of the Cited References

Strong *et al.*

The teachings of Strong *et al.* are discussed above.

Thorpe et al.

Thorpe *et al.* teaches using immunological reagents to target therapeutic or diagnostic agents to tumor-associated vascular endothelial cells (col. 4, lines 11-16). Thorpe *et al.* teaches various antibodies directed to VEGF (col. 83, line 11 through col. 84, line 36). Thorpe *et al.* teaches bi-specific antibodies having specificity for the targeted tumor cell antigen on the one hand and the targeted activating molecule on the other (col. 29, lines 25-30). Thorpe *et al.* teaches that bi-specific antibodies recognize a selected tumor cell surface antigen and a selected cytokine activating antigen on the surface of a selected leukocyte cell type such that the bi-specific construct will bind to tumor cells and cross-link the tumor cells with the leukocyte cells (col. 12, lines 16-44).

Thorpe *et al.* does not teach or suggest treating neovascular disease using a photosensitizing compound, nor does the reference teach or suggest a targeted photosensitizing compound that selectively binds to abnormal endothelium in the eye. Thorpe *et al.* does not teach or suggest administering a conjugate that includes a photoreactive compound and a targeting moiety that selectively binds to abnormal endothelium that lines or composes neovasculature tissue. Thorpe *et al.* does not teach or suggest allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue. Thorpe *et al.* does not teach or suggest selecting a combination of an intensity of light for illuminating and a

duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness because of the following.

The combination of teachings of Strong *et al.* with the teachings of Thorpe *et al.* does not result in the instantly claimed methods.

As discussed above, Strong *et al.* does not teach or suggest allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue, nor selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged.

Thorpe *et al.* does not cure these defects. Thorpe *et al.* does not teach or suggest treating neovascular disease using a conjugate that includes a photosensitizing compound. Thorpe *et al.* does not teach or suggest allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue. Thorpe *et al.* does not teach or suggest a photodynamic therapy or any intensity or duration of light to be used for photodynamic therapy. The reference does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Hence, even if, arguendo, Thorpe *et al.* teaches bi-specific antibodies, the combination of the teachings of Strong *et al.* and Thorpe *et al.* does not teach or suggest every element of claim 1 and its dependent claims.

Neither Strong *et al.* nor Thorpe *et al.*, alone or in combination, teaches or suggests allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue, nor selecting a combination of intensity of light used for irradiating and a duration of irradiation to produce a total fluence of the light

sufficient to activate the photosensitizer compound such that the target tissue is destroyed and the healthy non-target tissue remains undamaged. Thus, combining the teachings of Strong *et al.* and Thorpe *et al.* does not result in the subject matter of claims 1, 2, 11 and 12. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

It is respectfully submitted that the rejection of claims 1, 16 and 17 under 35 U.S.C. § 103(a) as unpatentable over Strong *et al.* in view of Thorpe *et al.* is overcome by the above remarks and should be withdrawn.

* * *

In view of the above, reconsideration and allowance of this application is respectfully requested.

Respectfully submitted,
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